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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,726	04/08/2004	Michael Wayne Graham	0763/74768-AAA/JPW/GJG/JR	1523

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COOPER & DUNHAM, LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
11/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,726	GRAHAM ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *134-154* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *134-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/08, 3/26/08 & 10/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 8, 2008 has been entered.

Petition for correction of inventorship

In view of the papers filed December 17, 2007, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by addition of inventors Peter Michael Waterhouse and Ming-Bo Wang.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claim Objections

Claims 146-149 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 134 recites a synthetic gene comprising first and second structural gene sequences that are 20-30 nucleotides in length and an optional stuffer fragment that is also defined (based on lines 20-22 of the claim) as 20-30 nucleotides in length. Claim 146 depends from claim 134 and fails to further limit because it recites that the first and second structural genes and the stuffer fragment together form an interrupted palindrome that is 20-30 nucleotides in length. Since both the first and second structural genes are each defined in claim 134 as at least 20 nucleotides, even if the stuffer fragment is not present the interrupted palindrome of claim 146 must be at least 40 nucleotides in length. Claims 147-149 each fail to further limit claim 134 because they define the stuffer fragment as having a length longer than that recited in claim 134.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 134, 135 and 142-154 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods for producing RNA capable of reducing expression of a target gene in a mammalian cell by administering a double stranded synthetic gene that comprises at least first and second structural genes, each of which are 20-30 nucleotides in length. The claims are directed broadly any target gene within a mammalian cell.

Applicants point to page 10 as providing support for the limitation that the structural gene sequences are 20-30 nucleotides in length. However, this portion of the specification does not disclose use of structural genes of 20-30 nucleotides to target any gene, page 10 specifically states that structural genes of this length are a preferred embodiment targeting specific genes: viral DNA or RNA polymerases, viral coat proteins, or visually-detectable genes involved in determining pigmentation, cell death or other external phenotype. The generic disclosure of targeting any endogenous, foreign and viral genes is also found on page 10, but requires 30 contiguous nucleotides of the target.

Because the specification teaches that use of structural gene sequences of 20-30 nucleotides is limited to certain viral genes and visually detectable genes associated with external phenotypes, the disclosure of the specification is not commensurate in

scope with the claimed invention and the claims do not satisfy the written description requirement.

Claim interpretation

Claim 134 recites that the first structural gene sequence is identical to the target gene and the second comprises nucleotides identical in sequence to, and in an inverted orientation relative to, the first structural gene sequence. Page 18 has been pointed to as providing support for the limitation "inverted orientation". This page of the specification says in part, "More preferably, the multiple structural gene unit comprises two identical or substantially identical structural genes ...in a head-to-tail configuration as a direct repeat or, alternatively, in a head-to-head configuration as an inverted repeat or palindrome." The inverted repeat resulting from a head-to-head configuration is shown in figure 14, which is described in example 3 on page 31,

> "Plasmid pCMV.BEV.VEB (FIG. 14) comprises an inverted repeat or palindrome of a complete BEV polymerase open reading frame under the control of the CMV-IE promoter sequence…To produce pCMV.BEV.VEB, the BEV polymerase structural gene from plasmid pCR.BEV.2 (FIG. 7) was sub-cloned in the antisense orientation as a *Bgl*II-to-*Bam*HI fragment into *Bam*HI-digested pCMV.BEV.2 (FIG. 10), immediately downstream of the BEV polymerase structural gene already present therein."

Based on the disclosure at pages 18 and 31, the configuration set forth in the instant claims is interpreted to be a first structural gene sequence in the sense orientation relative to the target gene and a second structural gene sequence in the antisense orientation, making the second structural gene sequence complementary to the target gene. Upon transcription, the individual structural gene sequences will hybridize to form a hairpin, or stem-loop, structure.

Claim Rejections - 35 USC § 103

Claims 134-154 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 5,605,559, of record) in view of Agrawal et al. (WO 94/01550, of record), Gold et al. (US 5,270,163), Kotin et al. (US 5,580,703) and Chatterjee et al. (US 5,474,935, of record).

The claims are directed to methods of producing RNAs that are capable of reducing expression of a gene in a mammalian cell by administering a double stranded synthetic gene that comprises first and second copies of a structural gene and an optional stuffer fragment that are 20-30 nucleotides in length. In specific embodiments, the target gene is in an exon, is a viral gene, an endogenous gene or a transgene and is targeted to the coding region or the UTR regions. Other embodiments recite the length of the stuffer fragment and how the double stranded synthetic gene is introduced.

Fire et al. teach and claim a method of inhibiting gene expression in cells, including animal cells, using double stranded RNAs. The double stranded RNA comprises a sequence complementary to a portion of the target gene and a sequence identical to a portion of the target gene, each of which is at least 25 nucleotides. Target genes include cellular genes, endogenous genes, transgenes and viral genes (see claims 1-6 and 10). At column 4, lines 41-46 Fire et al. teach that dsRNAs used in the invention can be formed from a single self-complementary RNA. At columns 8-9 and in claim 21 Fire et al. teach that RNA synthesis can be initiated *in vivo* or *in vitro* and that RNA can be produced by an expression construct. Fire et al. additionally teach at

column 9 that the dsRNA can be introduced to a cell in a variety of ways, including by lipid-mediated transport (i.e., a liposome) or within a viral particle comprising a viral vector. At column 10 Fire et al. teach that viruses can be targeted, including HIV. At column 5 Fire et al. teach that the dsRNA can target any gene and is not limited to any particular portion of the gene but do not explicitly teach targeting of the untranslated regions of a gene. Fire et al. do not explicitly claim the use of double stranded RNAs that comprise a stuffer fragment (i.e., a loop connecting the two portions of the RNA).

It was well known in the art at the time the invention was made that nucleic acids that are fully or partially self-complementary form hairpin structures having unpaired loop regions. For example, Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region and may comprise an unpaired loop region. This concept is also exemplified by Gold et al., who teach in the drawings several RNAs with stem-loop structures. At column 24, Gold et al. teach that the RNAs of their invention can be amplified by any known means, including the use of vectors administered to a host cell.

At the time the invention was made it was known to those of ordinary skill in the art that some viral vectors can integrate an exogenous sequence into the genome of a cell. See, for example, Kotin et al., who teach that AAV vectors integrate site-specifically into a host's genome and that this characteristic can be exploited for gene therapy (see column 1, lines 15-20 and column 4, line 50 through column 5, line 2).

At the time the invention was made the person of ordinary skill in the art recognized that different regions of genes, including the untranslated regions, are suitable targets for nucleic acid therapeutics. Chatterjee et al. teach constructs targeted to viral genes, explicitly teaching that lentiviruses such as HIV and DNA viruses such as HSV are suitable targets, teaching at column 4 that any viral gene whose sequence is known can be targeted. One of ordinary skill in the art would recognize that this includes the genes for coat proteins and polymerases. At column 3 Chatterjee et al. teach that antisense oligonucleotides targeted against areas of critical viral RNA transcripts including the 5'-untranslated region and splice sites (which are part of an exon) have demonstrated significant antiviral activities.

It would have been obvious to one of ordinary skill in the art at the time of invention to perform the method of inhibiting gene expression with double stranded RNA claimed by Fire et al. using a single self-complementary RNA formed by transcription of a synthetic gene sequence that comprises two copies of an RNA sequence in sense and antisense orientation and to use a sequence wherein each copy of the sequence is 20-30 nucleotides in length. Based on the claims of Fire et al. of using a duplex RNA that can comprise 25 nucleotides in each strand and can be produced from an expression construct, the teachings of Fire et al. that inhibitory double stranded RNA can be formed from a single self-complementary strand and the recognition by those in the art, as evidenced by Agrawal et al. and Gold et al., that self-complementary nucleotide strands form a hairpin comprising an unpaired loop, one of ordinary skill in the art would recognize the use of a hairpin RNA in place of a duplex of two strands and

the size of the loop is a matter of design choice and that use of a hairpin RNA allows for production of the RNA within a cell from an expression construct. One would further recognize that because Fire et al. explicitly teach delivering an RNA to a cell using a viral vector and Kotin et al. teach that AAV vectors will integrate into a host's genome, the use of the vector taught by Kotin et al. is a matter of simple substitution of one known type of vector for another. It would have further been obvious to produce RNA targeted to a viral gene and to target the untranslated regions of the gene. Fire et al. provide a motivation to target viral genes by specifically claiming such a target and Chatterjee et al. provide a motivation to target an untranslated region of a gene by teaching that targeting of such regions is proven to provide significant antiviral activity. Because the combination of the cited references provides a vector having the structural limitations of the claims and because administering this vector to a cell as taught by Fire et al. for the purpose of inhibiting gene expression would necessarily result in the production of a RNA capable of delaying, repressing or reducing expression of a target gene the invention of claims 134-154 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse the rejection of record by arguing that the Fire et al. reference claims the benefit of a provisional application filed December 23, 1997 and that this provisional discloses less than the non-provisional application. Applicants refer to a marked up copy of Fire et al. showing the differences between the patent and the

provisional, but provide no specific arguments regarding what is lacking in the provisional application and how such a lack relates to the rejection of record.

Applicants further argue that if the Fire et al. reference does not have the benefit of the provisional application it would not be prior art to the instant application. Applicants' attention is directed to the rejection as revised, which addresses how the claimed invention of Fire et al. also renders the instant claims obvious. In view of the revised rejection, it is noted that this reference can only be overcome by establishing priority of invention through interference proceedings.

Applicants argue that the combination of Fire et al. and Agrawal et al. does not teach or suggest synthetic genes having a repeated sequence of 20-30 nucleotides in length and further argue the claimed size range is an optimal range for mammalian cells that could not have been predicted from the prior art. This is not persuasive because Fire et al. specifically teach and claim use of double stranded RNAs of at least 25 nucleotides in length.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635